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ORIGINAL RESEARCH

The Role of ProBNP on Prognosis in Scorpion Stings

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Introduction—Scorpion stings are a major health problem with potentially fatal consequences. Children under the age of 10 y especially face a great risk. Predicting the prognosis is important in reducing mortality and morbidity because it enables the use of early treatment options. In this study, we examine the relationship between proBNP and prognosis in scorpion stings.

Methods—This is a retrospective analysis of patients aged ≤18 y who were admitted to the child emergency service with a scorpion sting. We examined the demographical data, clinical findings, laboratory records, treatments, and results of the patients. We classified stage 1 and stage 2 scorpion envenomation as group 1 (mild-moderate) and stage 3 and 4 as group 2 (severe). A *t* test was used for normally distributed data, and the Mann-Whitney U test was used for nonnormally distributed data. The correlation analysis was done using the Spearman test.

Results—There were 32 (74%) patients in the mild-moderate group and 11 (26%) in the severe group. ProBNP 1 was significantly higher in the severe group at admission (P=0.016). There was no difference between the troponin I values (P=0.051). ProBNP 2 (12th hour) and proBNP 3 (24th hour) were higher in the severe group (P=0.001 and P=0.032, respectively). There was a negative correlation between proBNP and echocardiographic findings involving ejection fraction and shortening fraction (r=–0.703, P=0.002).

Conclusions—In our study, the first proBNP values were significantly higher in the severe group. This suggests that proBNP may be beneficial in predicting prognosis.

Keywords: poisoning, BNP, venom, scorpionism, troponin I

Introduction

Approximately 1 to 1.5 million scorpion stings occur around the world annually, of which 3000 result in death.[1] Children and adolescents under the age of 10 y particularly face a great risk of scorpion envenomation.[2] Of the scorpions found in North Africa, the Middle East, Israel, Lebanon, Iran, and Turkey, *Leiurus* spp often cause damage that leads to autonomic dysfunction.[3] Alpha toxins in scorpion venom act by binding to sodium channels in the cell membrane and inhibiting action potential inactivation. This effect, through a synergistic effect with other ingredients in scorpion venom, causes the prolongation of depolarization and excessive release of acetylcholine from parasympathetic ganglia as well as excessive release of epinephrine and norepinephrine from sympathetic ganglia and the adrenal glands. Excessive release of these neurotransmitters results in an autonomic storm. Cholinergic findings are bronchore, salivation, sweating, bronchospasm, priapism, lacrimation, vomiting, diarrhea, and bradycardia. Hypertension, tachycardia, and agitation develop with sympathetic stimulation. Severe poisoning can cause direct myocardial damage, leading to arrhythmia, myocarditis, pulmonary edema, cardiogenic shock, and multisystem organ failure. It is believed that myocarditis occurring as a result of scorpion envenomation may be caused by increased catecholaminergic effect or through toxins directly affecting the heart muscle.[1]

Staging systems have been established to assess regional scorpion envenomation that causes autonomic storms. Accordingly, stage 1 has been defined as local

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effect only, stage 2 as systemic autonomic effects, stage 3 as cardiotoxicity including heart failure with cardiogenic shock or acute pulmonary edema with hypotension, and stage 4 as progressive cardiogenic shock with coma, seizure, or multiorgan failure.[2]

Natriuretic peptides are protein molecules released from the ventricles in response to volume or pressure load. Brain natriuretic peptide (BNP) is synthesized and released in the myocytes of the left ventricle, mainly in response to the volume expansion of the ventricle or the stretching of myocytes owing to pressure loading.[4] Initially, the hormone is released as pre-proBNP and splits into proBNP. ProBNP also dissociates into active BNP and inactive NT-proBNP.[5] BNP is a biologically active molecule that improves myocardial relaxation by causing natriuresis, vasodilation, and diuresis.[6]

In our study, we examined the demographic, clinical, and laboratory findings of patients who were admitted with scorpion stings. We aimed to evaluate cardiac enzymes and proBNP to show cardiac damage in scorpion stings.

Methods

We retrospectively analyzed patients aged ≤18 y who were admitted to Kahramanmaraş Sütçü İmam University Medical Faculty child emergency department and Kahramanmaraş Necip Fazıl city hospital child emergency service for scorpion sting between January 1, 2019 (the first case was on May 20, 2019) and October 31, 2019 (the last case was on August 26, 2019). Research approval was received from the ethics committee of Kahramanmaraş Sütçü İmam University medical faculty of medicine (2019/18-05). We were able to retrospectively access the medical records of patients from our center and Kahramanmaraş Necip Fazıl city hospital. We examined the demographic data, clinical findings, laboratory records, treatments, and results of the patients.

We divided the patients into 2 groups according to factors that can help in predicting poor prognosis. We classified stage 1 and 2 as group 1 (mild-moderate) and stage 3 and 4 as group 2 (severe). The patients were treated with antivenom produced by the Public Health Institution of the Republic of Turkey (Scorpion Antivenom, thsk.tglab@saglık.gov.tr). This antivenom contains immunoglobulins that neutralize *A crassicauda* venom. It also has a polyvalent effect and has the power to neutralize other scorpion venom. Each 1 mL of immunocerum contains immunoglobulin that neutralizes scorpion venom of ≥50 LD (lethal dose) *A crassicauda* species.

Table 1. Demographic and clinical parameters

Parameters	*Mild-moderate n (%)*	*Severe n (%)*	*P*[a]
Sex			
Female	15 (47)	5 (45)	0.93
Male	17 (53)	6 (55)	
Age (y)			
0–5	8 (25)	9 (82)	<0.05
6–10	10 (31)	1 (9)	
11–18	14 (44)	1 (9)	
Site of scorpion sting			
Head/Neck	2 (6)	0 (0)	0.69
Trunk	1 (3)	1 (10)	
Upper extremity	13 (41)	5 (50)	
Lower extremity	16 (50)	4 (40)	
Stings (n)			
1	28 (88)	10 (91)	0.92
2	4 (13)	0 (0)	
3	0 (0)	1 (9)	
Time of arrival at hospital (h)	1 (0.5)[b]	1(0)[b]	0.31
Length of hospital stay (d)	0.5 (2)	3 (1)	0.0
Mortality	No	No	

[a]Mann-Whitney U test or χ^2 test.
[b]Median (interquartile ratio).

STATISTICAL ANALYSIS

The data obtained in the study were produced using SPSS version 25 (IBM SPSS Statistics 25). Categorical variables were expressed as numbers and percentages and numerical variables as median and interquartile values. Categorical variables between groups were compared using the χ^2 test. Normality of numerical data was evaluated through the Kolmogorov-Smirnov test. Normally distributed data were compared with the *t* test, and nonnormally distributed data were compared using the Mann-Whitney U test. The correlation analysis was done using the Spearman test. Statistical significance was accepted as $P<0.05$.

Results

The data of 43 patients who were monitored for scorpion stings were analyzed. The demographic data of the patients are presented in Table 1. The patients and their families described the scorpion responsible for the stinging. Usually, the scorpions that stung the patients were killed by families. We classified stage 1 and stage 2 scorpion poisoning as group 1 and stage 3 and 4 as group 2 according to factors that can help in predicting poor

Table 2. Drugs given to patients

Patient no.	*Antivenom* (*1 vial: 1 mL*)	*Adrenaline* ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	*Dobutamine* ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	*Milrinone* ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	*Doxazosine* ($mg \cdot kg^{-1}$)
8	1	0.2	10		
21	1	0.2	10	0.2	0.03
32	2				0.03
28	2				0.03
38	1				0.03
16	1				
40	1	0.2			0.03
17	1				
33	1				0.03
34	1				
23	1				

prognosis. There were 32 (74%) patients in the mild-moderate group and 11 (26%) in the severe group. The median age of the mild-moderate group was 9.75 y (Q1=5.0, Q3=14), and the median age of the severe group was 3.75 y (Q1=2.0, Q3=5.0). The median weight of the mild-moderate group was 28 kg (Q1=18.25, Q3=46.75), and the median weight of the severe group was 15 kg (Q1=13, Q3=27). The severe group had lower body weight (P=0.018). The time to admission to the hospital was not different between the groups (P=0.31). There was also no difference between the groups in terms of the site of the scorpion sting and the number of stings (P=0.64 and P=0.84, respectively). The most common finding was localized pain. Vomiting was present in 1 patient in the mild-moderate group and 6 patients in the severe group. There was syncope present in 1 patient, sweating in 1 patient, and dizziness and abdominal pain in 1 patient. Compartment syndrome developed in 1 patient. Fourteen patients initially had hypertension during admission, and 2 patients had hypotension and hypothermia. The 2 patients with hypotension and hypothermia were followed up for pulmonary edema. There was no difference in hypertension between the groups (P=0.75). Three patients had sinus tachycardia.

One vial of antivenom was given to all patients with systemic involvement, and 2 vials were given to 2 patients in the severe group. Along with the administration of antivenom, steroids and antihistamines were administered to the patients. The patients did not develop a reaction against antivenom treatment. Depending on the patient's clinical condition, other drugs were given, as shown in Table 2. One patient received adrenaline and dobutamine; 1 patient received adrenaline, dobutamine, milrinone, and doxazoin; and 1 patient received adrenaline and doxazosin. Six patients were given doxazosin in total.

Laboratory findings are shown in Table 3. Leukocytosis, hyperglycemia, and transaminase levels were found to be high in the severe group (P=0.002, P=0.003, and P=0.001 for AST (aspartat aminotransferase); P=0.008 for ALT (alanin aminotransferase)). In the blood gas analysis, although pH, HCO3, and base excess were different in the severe group, there was no difference between the groups in terms of lactate and pCO2 (P=0.000, P=0.003, P=0.005, P=0.59, and P=0.12, respectively). Thrombocytosis was not observed in our patients at the time of first admission (P=0.14). There was no difference between the groups in terms of electrocardiographic findings.

In the blood samples taken at the time of first admission, there was no difference between troponin I values (0th hour) (P=0.051) (Figure 1). ProBNP 1 (0th hour) was significantly higher in the severe group (P=0.016) (Figures 2 and 3). In blood samples taken 12 h and 24 h after the first admission, proBNP 2 (12th hour) and proBNP 3 were higher in the severe group (P=0.001; P=0.032, respectively). Troponin I (12th hour) was high enough to make a difference in the severe group, whereas troponin I (24th hour) was not different (P=0.011 and P=0.84, respectively). In terms of echocardiographic findings (Table 4), the ejection fraction and shortening fraction were significantly lower in the severe group (P=0.006 and P=0.005, respectively). There was a negative correlation between proBNP and echocardiographic findings involving ejection fraction and shortening fraction (r=–0.703, P=0.002).

Discussion

Cardiopulmonary complications are frequently the cause of death in envenomation related to scorpion stings.[7] Autonomic storm is generally observed in scorpion sting cases in our country, and the follow-up and treatment are arranged according to autonomic storm.[3] In a study with 64 patients in Turkey, the death rate was 12%;

Table 3. Laboratory results

	Mild/Moderate median (IQR)	*Severe median (IQR)*	*P Mann-Whitney U test*
White blood cell ($10^3 \cdot mL^{-1}$)	9595 (4995)	24330 (20160)	0.002
Neutrophile ($10^3 \cdot mL^{-1}$)	5050 (3735)	10330 (12080)	0.012
Lymphocyte ($10^3 \cdot mL^{-1}$)	3505 (3553)	3020 (13760)	0.38
Hemoglobin ($g \cdot dL^{-1}$)	13 (1.45)	12.2 (1.7)	0.35
Platelets ($10^9 \cdot mL^{-1}$)	305000 (124750)	363000 (276000)	0.14
Glucose ($mg \cdot dL^{-1}$)	106 (20)	128 (126)	0.003
BUN ($mg \cdot dL^{-1}$)	16.4 (21.2)	19.3 (18.8)	0.34
Creatinine ($mg \cdot dL^{-1}$)	0.43 (0.33)	0.40 (0.23)	0.27
Aspartate transaminase ($U \cdot L^{-1}$)	25.5 (11.5)	35 (6.5)	0.001
Alanine transaminase ($U \cdot L^{-1}$)	15 (7)	22 (23)	0.008
Uric acid ($mg \cdot dL^{-1}$)	3.6 (1.3)	5 (0)	0.033
pH	7.39 (0.05)	7.34 (0.09)	0.000
pCO_2 (mm Hg)	42.5 (7)	37.1 (6)	0.12
HCO^3 ($mmol \cdot L^{-1}$)	24.8 (2.8)	18.5 (5.2)	0.003
Base excess	1.49 (4.3)	–7.8 (7.7)	0.005
Lactate ($mmol \cdot L^{-1}$)	1.8 (1.0)	1.5 (2.9)	0.59
ProBNP 1 (0 h) ($ng \cdot L^{-1}$)	69 (7)	349 (33)	0.016
ProBNP 2 (12 h)	221 (21)	3070 (777)	0.001
ProBNP 3 (24 h)	191 (18)	447 (1056)	0.032
Troponin-I 1 (0 h) ($\mu g \cdot L^{-1}$)	0.01 (0.0)	0.02 (0.07)	0.051
Troponin-I 2 (12 h)	0.01 (0.0)	0.1 (0.11)	0.011
Troponin-I 3 (24 h)	0.05 (0.11)	0.31 (0.28)	0.84
Creatinine kinase 1 (0 h) ($U \cdot L^{-1}$)	144 (134)	336 (238)	0.006
Creatinine kinase 2 (12 h) ($U \cdot L^{-1}$)	90 (76)	370 (506)	0.005
Creatinine kinase 3 (24 h) ($U \cdot L^{-1}$)	50.5 (15)	310 (282)	0.004

BUN, blood urea nitrogen; IQR, interquartile ratio.

the death rate in another study was reported as 0%.[8,9] Similarly, none of the patients in our research died (0%). So far, 13 species from 8 families have been identified, including Buthidae, Chacthida, Iurida, and Scorpionidae families in Turkey. *Androctonus crassicauda* and *Leiurus quinquestriatus*, which are members of the Buthidea family, are usually seen in Kahramanmaraş.[10] Recently, a new yellow scorpion species named *Leirus abdullahbayrami* has been reported in Kahramanmaraş.[11,12]

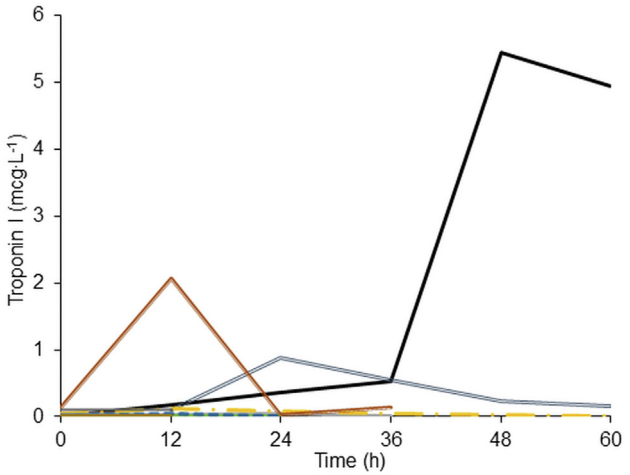

Figure 1. Troponin I levels in patients in the severe group.

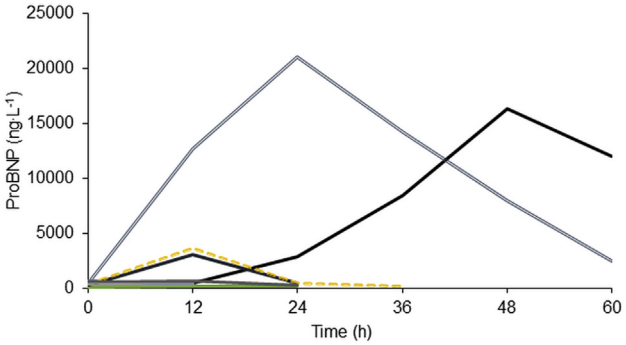

Figure 2. ProBNP levels in patients in the severe group.

In our study, because the patients described the scorpions that stung them as being yellow and black, it was presumed that the black scorpion is *Androctonus crassicauda* and the yellow *Leiurus quinquestriatus* or *Leirus abdullahbayrami*, in line with previous studies, although the species distinction was not made in accordance with the patients' clinical results.

In this research, hypertension was observed in 14 (33%) patients, and there was no statistically significant difference between the mild-moderate and severe groups. Although thrombocytosis was suggested as a marker of clinical deterioration in a previous study, our study found, in accordance with the literature, that thrombocytosis was not observed at the time of first presentation.[3,13,14] BNP and NT-BNP may be elevated in patients with myocarditis.[15] In 1 study, proBNP levels were evaluated in scorpion-associated myocarditis, and it was suggested that serial proBNP monitoring might be important in scorpion poisoning and that further studies should be conducted on the topic.[16] In our study, proBNP was observed to be elevated without significant troponin I elevation. However, there was a difference between the second troponin I values taken at the 12th hour. This shows that the proBNP value is important during early admission for predicting the prognosis of scorpion stings. Thus, we suggest that proBNP can be an important parameter in terms of directing prognosis, follow-up, and treatment in scorpion stings.

In previous studies, a reduction in ejection fraction was detected in patients stung by scorpions.[17] In our study, echocardiography was performed on all patients in the first hour after admission to the hospital. The ejection fraction was significantly lower in the severe group. The shortening fraction was also significantly lower in the severe group. A significant negative correlation was found between proBNP and ejection fraction and

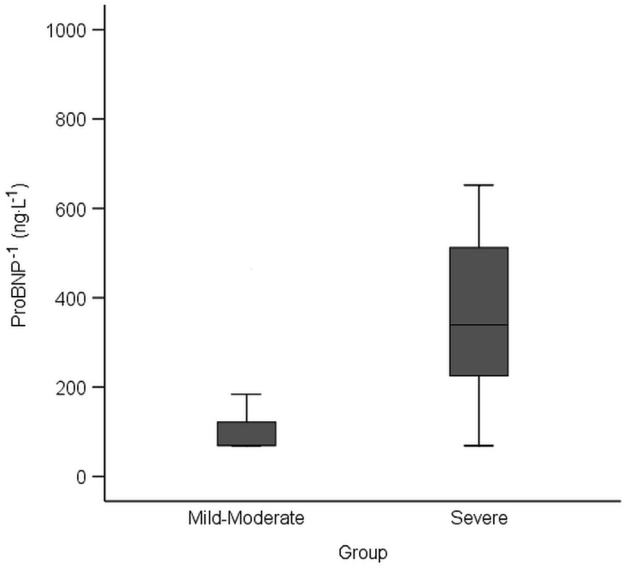

Figure 3. ProBNP levels in at first admission between groups. ProBNP levels were higher at the time of first admission in the severe group.

Table 4. ECHO and ECG results

	Mild/Moderate[a]	*Severe*[a]	*P*[b]
ECG			
Heart rate (beats·min^{-1})	91 (41)	110 (63)	0.30
QTc (s)	0.39 (0.03)	0.38 (0.03)	0.47
Echo			
EF (%)	76 (7)	68 (9)	0.006
SF (%)	43 (6)	35.5 (8)	0.005

ECG, electrocardiography; ECHO, echocardiography; EF, ejection fraction; IQR, interquartile ratio; SF, shortening fraction.
[a]Median (IQR).
[b]Mann Whitney U test.

shortening fraction. This shows that the higher the proBNP, the more severe the cardiac involvement can be. In addition, the initial proBNP value can predict prognosis and show whether the patient should be referred to advanced centers. It is believed that patients with high proBNP will require a longer intensive care stay because prognosis will be poor.

LIMITATIONS

The retrospective nature of our study and the low number of patients constitute the limitations of our study. Our data were limited to what was recorded on the patient records. The envenoming scorpion was determined by the descriptions provided by patients and their relatives. Prospective studies with a higher number of cases are needed to address the deficiencies in our study.

Conclusions

At the time of initial hospital admission, proBNP may be more useful than troponin I in predicting the prognosis.

Author Contributions: Study concept and design (UUG, Sİ); acquisition of the data (SD, TD, SY); analysis of the data (Sİ); drafting of the manuscript (UUG, Sİ, TD); critical revision of the manuscript (UUG, Sİ); approval of final manuscript (Sİ, UUG, SD, SY, EA).
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